



Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease

Citation

Jostins, Luke, Stephan Ripke, Rinse K Weersma, Richard H Duerr, Dermot P McGovern, Ken Y Hui, James C Lee, et al. 2012. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 491(7422): 119-124.

Published Version

doi:10.1038/nature11582

Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:11181023>

Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

Published in final edited form as:

Nature. 2012 November 1; 491(7422): 119–124. doi:10.1038/nature11582.

Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease

Luke Jostins^{1,*}, Stephan Ripke^{2,3,*}, Rinse K Weersma^{4,†}, Richard H Duerr^{5,6,‡}, Dermot P McGovern^{7,8,‡}, Ken Y Hui⁹, James C Lee¹⁰, L Philip Schumm¹¹, Yashoda Sharma¹², Carl A Anderson¹, Jonah Essers¹³, Mitja Mitrovic^{14,15}, Kaida Ning¹², Isabelle Cleynen¹⁶, Emilie Theate^{17,18}, Sarah L Spain¹⁹, Soumya Raychaudhuri^{20,21,22}, Philippe Goyette²³, Zhi Wei²⁴, Clara Abraham¹², Jean-Paul Achkar^{25,26}, Tariq Ahmad²⁷, Leila Amininejad²⁸, Ashwin N Ananthakrishnan²⁹, Vibeke Andersen³⁰, Jane M Andrews³¹, Leonard Baidoo⁵, Tobias Balschun³², Peter A Bampton³³, Alain Bitton³⁴, Gabrielle Boucher²³, Stephan Brand³⁵, Carsten Büning³⁶, Ariella Cohain³⁷, Sven Cichon³⁸, Mauro D'Amato³⁹, Dirk De Jong⁴, Kathy L Devaney²⁹, Marla Dubinsky⁴⁰, Cathryn Edwards⁴¹, David Ellinghaus³², Lynnette R Ferguson⁴², Denis Franchimont²⁸, Karin Fransen^{5,43}, Richard Gearry^{44,45}, Michel Georges¹⁷, Christian Gieger⁴⁶, Jürgen Glas³⁴, Talin Haritunians⁸, Ailsa Hart⁴⁷, Chris Hawkey⁴⁸, Matija Hedl¹², Xinli Hu²⁰, Tom H Karlsen⁴⁹, Limas Kupcinskis⁵⁰, Subra Kugathasan⁵¹, Anna Latiano⁵², Debby Laukens⁵³, Ian C Lawrance⁵⁴, Charlie W Lees⁵⁵, Edouard Louis¹⁸, Gillian Mahy⁵⁶, John Mansfield⁵⁷, Angharad R Morgan⁴², Craig Mowat⁵⁸, William Newman⁵⁹, Orazio Palmieri⁵², Cyriel Y Ponsioen⁶⁰, Uros Potocnik^{14,61}, Natalie J Prescott⁶², Miguel Regueiro⁵, Jerome I Rotter⁸, Richard K Russell⁶³, Jeremy D Sanderson⁶⁴, Miquel Sans^{65,66}, Jack Satsangi⁵⁵, Stefan Schreiber^{67,68}, Lisa A Simms⁶⁹, Jurgita Sventoraityte⁵⁰, Stephan R Targan⁷, Kent D Taylor^{7,8}, Mark Tremelling⁷⁰, Hein W Verspaget⁷¹, Martine De Vos⁵³, Cisca Wijmenga⁴³, David C Wilson^{63,72}, Juliane Winkelmann⁷³, Ramnik J Xavier^{29,74}, Sebastian Zeissig⁷⁵, Bin Zhang³⁷, Clarence K Zhang⁷⁶, Hongyu Zhao⁷⁶, The International IBD Genetics Consortium⁷⁷, Mark S Silverberg⁷⁸, Vito Annese^{52,79}, Hakon Hakonarson^{80,81}, Steven R Brant⁸², Graham Radford-Smith^{69,83}, Christopher G Mathew^{19,‡}, John D Rioux^{23,‡}, Eric E Schadt^{37,‡}, Mark J Daly^{2,3,‡}, Andre Franke^{32,‡}, Miles Parkes^{10,‡}, Severine Vermeire^{85,‡}, Jeffrey C Barrett^{1,†}, and Judy H Cho^{9,12,†}

Correspondence and requests for materials should be addressed to JHC (judy.cho@yale.edu).

*denotes equal contributions

†denotes equal contributions

‡denotes equal contributions

⁷⁷A full list of consortium members is provided in the Supplementary Note

Author Contributions Conceived and designed study, managed study and funding: JHC, JCB, RKW, RHD, DPM, MDA, VA, AF, MP, SV. Manuscript preparation: JHC, JCB, LJ, SR, RKW, RHD, DPM, MJD, MP, CGM. Performed or supervised statistical and computational analyses: JHC, JCB, LJ, SR, RKW, KYH, CAA, JE, KN, SLS, SR, ZW, CA, AC, GB, MH, XH, BZ, CKZ, HZ, JDR, EES, MJD. Study subject recruitment and assembled phenotypic data: RKW, RHD, DPM, JCL, LPS, YS, PG, JPA, TA, LA, ANA, VA, JMA, LB, PAB, AB, SB, CB, SC, MDA, DDJ, KLD, MD, CE, LRF, DF, MG, RG, JG, AH, CH, THK, LK, SK, AL, DL, EL, ICL, CWL, ARM, CM, GM, JM, WN, OP, CYP, UP, NJP, MR, JIR, RKR, JDS, MS, JS, SS, LAS, JS, SRT, MT, HWV, MDV, CW, DCW, JW, RJX, SZ, MSS, VA, HH, SRB, JDR, GRS, CGM, AF, MP, SV, JHC. Established DNA collections, genotyping and data management: RKW, RHD, DPM, LPS, YS, MM, IC, ET, TB, DE, KF, TH, KDT, CGM, AF, MP, JHC. All authors read and approved the final manuscript before submission.

Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Data have been deposited in NCBI's database of Genotypes and Phenotypes (dbGaP) through study accession numbers phs000130.v1.p1 and phs000345.v1.p1. Summary statistics for imputed GWAS are available at <http://www.broadinstitute.org/mpg/ricopili/>. Summary statistics for the meta-analysis markers are available at <http://www.ibdgenetics.org/>. The 523 causal gene network cytoscape file is available on request. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at www.nature.com/nature.

¹Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
²Analytic and Translational Genetics Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA ³Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA ⁴Department of Gastroenterology and Hepatology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands ⁵Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA ⁶Department of Human Genetics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, USA ⁷Cedars-Sinai F. Widjaja Inflammatory Bowel and Immunobiology Research Institute, Los Angeles, California, USA ⁸Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA ⁹Department of Genetics, Yale School of Medicine, New Haven, Connecticut, USA ¹⁰Inflammatory Bowel Disease Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK ¹¹Department of Health Studies, University of Chicago, Chicago, Illinois, USA ¹²Department of Internal Medicine, Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut, USA ¹³Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA ¹⁴University of Maribor, Faculty of Medicine, Center for Human Molecular Genetics and Pharmacogenomics, Maribor, Slovenia ¹⁵University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands ¹⁶Department of Pathophysiology, Gastroenterology section, KU Leuven, Leuven, Belgium ¹⁷Unit of Animal Genomics, Groupe Interdisciplinaire de Genoproteomique Appliquee (GIGA-R) and Faculty of Veterinary Medicine, University of Liege, Liege, Belgium ¹⁸Division of Gastroenterology, Centre Hospitalier Universitaire, Universite de Liege, Liege, Belgium ¹⁹Department of Medical and Molecular Genetics, King's College London School of Medicine, Guy's Hospital, London, UK ²⁰Division of Rheumatology Immunology and Allergy, Brigham and Women's Hospital, Boston, Massachusetts, USA ²¹Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA ²²Division of Genetics, Brigham and Women's Hospital, Boston, Massachusetts, USA ²³Université de Montréal and the Montreal Heart Institute, Research Center, Montréal, Québec, Canada ²⁴Department of Computer Science, New Jersey Institute of Technology, Newark, NJ 07102, USA ²⁵Department of Gastroenterology & Hepatology, Digestive Disease Institute, Cleveland Clinic, Cleveland, Ohio ²⁶Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA ²⁷Peninsula College of Medicine and Dentistry, Exeter, UK ²⁸Erasmus Hospital, Free University of Brussels, Department of Gastroenterology, Brussels, Belgium ²⁹Massachusetts General Hospital, Harvard Medical School, Gastroenterology Unit, Boston, Massachusetts, USA ³⁰Viborg Regional Hospital, Medical Department, Viborg, Denmark ³¹Inflammatory Bowel Disease Service, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, and School of Medicine, University of Adelaide, Adelaide, Australia ³²Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany ³³Department of Gastroenterology and Hepatology, Flinders Medical Centre and School of Medicine, Flinders University, Adelaide, Australia ³⁴Division of Gastroenterology, McGill University Health Centre, Royal Victoria Hospital, Montréal, Québec, Canada ³⁵Department of Medicine II, University Hospital Munich-Grosshadern, Ludwig-Maximilians-University, Munich, Germany ³⁶Department of Gastroenterology, Charit, Campus Mitte, Universitätsmedizin Berlin, Berlin, Germany ³⁷Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York City, New York, USA ³⁸Department of Genomics, Life & Brain Center, University Hospital Bonn, Bonn, Germany ³⁹Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden ⁴⁰Department of Pediatrics, Cedars Sinai Medical Center, Los Angeles, California, USA ⁴¹Torbay Hospital, Department of Gastroenterology, Torbay, Devon, UK ⁴²School of Medical Sciences, Faculty of Medical & Health Sciences, The University of Auckland, Auckland, New Zealand ⁴³University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands ⁴⁴Department of Medicine, University of Otago, Christchurch, New Zealand ⁴⁵Department of

Gastroenterology, Christchurch Hospital, Christchurch, New Zealand ⁴⁶Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany ⁴⁷St Mark's Hospital, Watford Road, Harrow, Middlesex, HA1 3UJ ⁴⁸Nottingham Digestive Diseases Centre, Queens Medical Centre, Nottingham NG7 1AW, UK ⁴⁹Research Institute of Internal Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway ⁵⁰Kaunas University of Medicine, Department of Gastroenterology, Kaunas, Lithuania ⁵¹Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA ⁵²Unit of Gastroenterology, Istituto di Ricovero e Cura a Carattere Scientifico-Casa Sollievo della Sofferenza (IRCCS-CSS) Hospital, San Giovanni Rotondo, Italy ⁵³Ghent University Hospital, Department of Gastroenterology and Hepatology, Ghent, Belgium ⁵⁴School of Medicine and Pharmacology, The University of Western Australia, Fremantle, Australia ⁵⁵Gastrointestinal Unit, Molecular Medicine Centre, University of Edinburgh, Western General Hospital, Edinburgh, UK ⁵⁶Department of Gastroenterology, The Townsville Hospital, Townsville, Australia ⁵⁷Institute of Human Genetics, Newcastle University, Newcastle upon Tyne, UK ⁵⁸Department of Medicine, Ninewells Hospital and Medical School, Dundee, UK ⁵⁹Genetic Medicine, MAHSC, University of Manchester, Manchester, UK ⁶⁰Academic Medical Center, Department of Gastroenterology, Amsterdam, The Netherlands ⁶¹University of Maribor, Faculty for Chemistry and Chemical Engineering, Maribor, Slovenia ⁶²King's College London School of Medicine, Guy's Hospital, Department of Medical and Molecular Genetics, London, UK ⁶³Royal Hospital for Sick Children, Paediatric Gastroenterology and Nutrition, Glasgow, UK ⁶⁴Guy's & St. Thomas' NHS Foundation Trust, St. Thomas' Hospital, Department of Gastroenterology, London, UK ⁶⁵Department of Gastroenterology, Hospital Clínic/Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain ⁶⁶Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBER EHD), Barcelona, Spain ⁶⁷Christian-Albrechts-University, Institute of Clinical Molecular Biology, Kiel, Germany ⁶⁸Department for General Internal Medicine, Christian-Albrechts-University, Kiel, Germany ⁶⁹Inflammatory Bowel Diseases, Genetics and Computational Biology, Queensland Institute of Medical Research, Brisbane, Australia ⁷⁰Norfolk and Norwich University Hospital ⁷¹Department of Gastroenterology, Leiden University Medical Center, Leiden, The Netherlands ⁷²Child Life and Health, University of Edinburgh, Edinburgh, Scotland, UK ⁷³Institute of Human Genetics and Department of Neurology, Technische Universität München, Munich, Germany ⁷⁴Center for Computational and Integrative Biology, Massachusetts General Hospital, Boston, Massachusetts, USA ⁷⁵Department for General Internal Medicine, Christian-Albrechts-University, Kiel, Germany ⁷⁶Department of Biostatistics, School of Public Health, Yale University, New Haven, Connecticut, USA ⁷⁸Mount Sinai Hospital Inflammatory Bowel Disease Centre, University of Toronto, Toronto, Ontario, Canada ⁷⁹Azienda Ospedaliero Universitaria (AOU) Careggi, Unit of Gastroenterology SOD2, Florence, Italy ⁸⁰Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA ⁸¹Department of Pediatrics, Center for Pediatric Inflammatory Bowel Disease, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA ⁸²Meyerhoff Inflammatory Bowel Disease Center, Department of Medicine, School of Medicine, and Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA ⁸³Department of Gastroenterology, Royal Brisbane and Womens Hospital, and School of Medicine, University of Queensland, Brisbane, Australia ⁸⁴Inflammatory Bowel Disease Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK ⁸⁵Division of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium

Abstract

Crohn's disease (CD) and ulcerative colitis (UC), the two common forms of inflammatory bowel disease (IBD), affect over 2.5 million people of European ancestry with rising prevalence in other populations¹. Genome-wide association studies (GWAS) and subsequent meta-analyses of CD and UC^{2,3} as separate phenotypes implicated previously unsuspected mechanisms, such as autophagy⁴,

in pathogenesis and showed that some IBD loci are shared with other inflammatory diseases⁵. Here we expand knowledge of relevant pathways by undertaking a meta-analysis of CD and UC genome-wide association scans, with validation of significant findings in more than 75,000 cases and controls. We identify 71 new associations, for a total of 163 IBD loci that meet genome-wide significance thresholds. Most loci contribute to both phenotypes, and both directional and balancing selection effects are evident. Many IBD loci are also implicated in other immune-mediated disorders, most notably with ankylosing spondylitis and psoriasis. We also observe striking overlap between susceptibility loci for IBD and mycobacterial infection. Gene co-expression network analysis emphasizes this relationship, with pathways shared between host responses to mycobacteria and those predisposing to IBD.

We conducted an imputation-based association analysis using autosomal genotype level data from 15 GWAS of CD and/or UC (Supplementary Table 1, Supplementary Figure 1). We imputed 1.23 million SNPs from the HapMap3 reference set (Supplementary Methods), resulting in a high quality dataset with reduced genome-wide inflation (Supplementary Figures 2, 3) compared with previous meta-analyses of subsets of these data^{2,3}. The imputed GWAS data identified 25,075 SNPs that had association $p < 0.01$ in at least one of the CD, UC or all IBD analyses. A meta-analysis of GWAS data with ImmunoChip⁶ validation genotypes from an independent, newly-genotyped set of 14,763 CD cases, 10,920 UC cases, and 15,977 controls was performed (Supplementary Table 1, Supplementary Figure 1). Principal components analysis resolved geographic stratification, as well as Jewish and non-Jewish ancestry (Supplementary Figure 4), and significantly reduced inflation to a level consistent with residual polygenic risk, rather than other confounding effects (from $\lambda_{GC} = 2.00$ to $\lambda_{GC} = 1.23$ when analyzing all IBD samples, Supplementary Methods, Supplementary Figure 5).

Our meta-analysis of the GWAS and ImmunoChip data identified 193 statistically independent signals of association at genome-wide significance ($p < 5 \times 10^{-8}$) in at least one of the three analyses (CD, UC, IBD). Since some of these signals (Supplementary Figure 6) probably represent associations to the same underlying functional unit, we merged these signals (Supplementary Methods) into 163 regions, of which 71 are reported here for the first time (Table 1, Supplementary Table 2). Figure 1A shows the relative contributions of each locus to the total variance explained in UC and CD. We have increased the total disease variance explained (variance being subject to fewer assumptions than heritability⁷) from 8.2% to 13.6% in CD and from 4.1% to 7.5% in UC (Supplementary Methods). Consistent with previous studies, our IBD risk loci seem to act independently, with no significant evidence of deviation from an additive combination of log odds ratios.

Our combined genome-wide analysis of CD and UC enables a more comprehensive analysis of disease specificity than was previously possible. A model selection analysis (Supplementary Methods 1d) showed that 110/163 loci are associated with both disease phenotypes; 50 of these have an indistinguishable effect size in UC and CD, while 60 show evidence of heterogeneous effects (Table 1). Of the remaining loci, 30 are classified as CD-specific and 23 as UC-specific. However, 43 of these 53 show the same direction of effect in the non-associated disease (Figure 1B, overall $p = 2.8 \times 10^{-6}$). Risk alleles at two CD loci, *PTPN22* and *NOD2*, show significant ($p < 0.005$) protective effects in UC, exceptions that may reflect biological differences between the two diseases. This degree of sharing of genetic risk suggests that nearly all the biological mechanisms involved in one disease play some role in the other.

The large number of IBD associations, far more than reported for any other complex disease, increases the power of network-based analyses to prioritize genes within loci. We investigated the IBD loci using functional annotation and empirical gene network tools

(Supplementary Table 2). Compared with previous analyses which identified candidate genes in 35% of loci^{2,3} our updated GRAIL⁸ -connectivity network identifies candidates in 53% of loci, including increased statistical significance for 58 of the 73 candidates from previous analyses. The new candidates come not only from genes within newly identified loci, but also integrate additional genes from previously established loci (Figure 1C). Only 29 IBD-associated SNPs are in strong linkage disequilibrium ($r^2 > 0.8$) with a missense variant in the 1000 Genomes Project data, which reinforces previous evidence that a large fraction of risk for complex disease is driven by non-coding variation. In contrast, 64 IBD-associated SNPs are in linkage disequilibrium with variants known to regulate gene expression (Supplementary Table 2). Overall, we highlighted a total of 300 candidate genes in 125 loci, of which 39 contained a single gene supported by two or more methods.

Seventy percent (113/163) of the IBD loci are shared with other complex diseases or traits, including 66 among the 154 loci previously associated with other immune-mediated diseases⁹, which is 8.6 times the number that would be expected by chance (Figure 2A, $p < 10^{-16}$, Supplementary Figure 7). Such enrichment cannot be attributed to the immune-mediated focus of the Immunochip, (Supplementary Methods 4a(i), Supplementary Figure 8), since the analysis is based on our combined GWAS-Immunochip data. Comparing overlaps with specific diseases is confounded by the variable power in studies of different diseases. For instance, while type 1 diabetes (T1D) shares the largest number of loci (20/39, 10-fold enrichment) with IBD, this is partially driven by the large number of known T1D associations. Indeed, seven other immune-mediated diseases show stronger enrichment of overlap, with the largest being ankylosing spondylitis (8/11, 13-fold) and psoriasis (14/17, 14-fold).

IBD loci are also markedly enriched (4.9-fold, $p < 10^{-4}$) in genes involved in primary immunodeficiencies (PIDs, Figure 2A), which are characterized by a dysfunctional immune system resulting in severe infections¹⁰. Genes implicated in this overlap correlate with reduced levels of circulating T-cells (*ADA*, *CD40*, *TAP1/2*, *NBS1*, *BLM*, *DNMT3B*), or of specific subsets such as Th17 (*STAT3*), memory (*SP110*), or regulatory T-cells (*STAT5B*). The subset of PIDs genes leading to Mendelian susceptibility to mycobacterial disease (MSMD)^{10–12} is enriched still further; six of the eight known autosomal genes linked to MSMD are located within IBD loci (*IL12B*, *IFNGR2*, *STAT1*, *IRF8*, *TYK2* and *STAT3*, 46-fold enrichment, $p = 1.3 \times 10^{-6}$), and a seventh, *IFNGR1*, narrowly missed genome-wide significance ($p = 6 \times 10^{-8}$). Overlap with IBD is also seen in complex mycobacterial disease; we find IBD associations in 7/8 loci identified by leprosy GWAS¹³, including 6 cases where the same SNP is implicated. Furthermore, genetic defects in *STAT3*^{14–15} and *CARD9*¹⁶, also within IBD loci, lead to PIDs involving skin infections with staphylococcus and candidiasis, respectively. The comparative effects of IBD and infectious disease susceptibility risk alleles on gene function and expression is summarized in Supplementary Table 3, and include both opposite (e.g. *NOD2* and *STAT3*, Supplementary Figure 9) and similar (e.g., *IFNGR2*) directional effects.

To extend our understanding of the fundamental biology of IBD pathogenesis we conducted searches across the IBD locus list: (i) for enrichment of specific GeneOntology (GO) terms and canonical pathways, (ii) for evidence of selective pressure acting on specific variants and pathways, and (iii) for enrichment of differentially expressed genes across immune cell types. We tested the 300 prioritized genes (see above) for enrichment in GO terms (Supplementary Methods) and identified 286 GO terms and 56 pathways demonstrating significant enrichment in genes contained within IBD loci (Supplementary Table 4, Supplementary Figure 10,11). Excluding high-level GO categories such as “immune system processes” ($p = 3.5 \times 10^{-26}$), the most significantly enriched term is regulation of cytokine production ($p = 2.7 \times 10^{-24}$), specifically IFNG- γ , IL-12, TNF- α , and IL-10 signalling.

Lymphocyte activation was the next most significant ($p=1.8 \times 10^{-23}$), with activation of T-, B-, and NK-cells being the strongest contributors to this signal. Strong enrichment was also seen for response to molecules of bacterial origin ($p=2.4 \times 10^{-20}$), and for KEGG's JAK-STAT signalling pathway ($p = 4.8 \times 10^{-15}$). We note that no enriched terms or pathways showed specific evidence of CD- or UC-specificity.

As infectious organisms are known to be among the strongest agents of natural selection, we investigated whether the IBD-associated variants are subject to selective pressures (Supplementary Methods, Supplementary Table 5). Directional selection would imply that the balance between these forces shifted in one direction over the course of human history, whereas balancing selection would suggest an allele frequency dependent-scenario typified by host-microbe co-evolution, as can be observed with parasites. Two SNPs show Bonferroni-significant selection: the most significant signal, in *NOD2*, is under balancing selection ($p = 5.2 \times 10^{-5}$), and the second most significant, in the receptor *TNFRSF18*, showed directional selection ($p = 8.9 \times 10^{-5}$). The next most significant variants were in the ligand of that receptor, *TNFSF18* (directional, $p = 5.2 \times 10^{-4}$), and *IL23R* (balancing, $p = 1.5 \times 10^{-3}$). As a group, the IBD variants show significant enrichment in selection (Figure 2B) of both types ($p = 5.5 \times 10^{-6}$). We discovered an enrichment of balancing selection (Figure 2B) in genes annotated with the GO term “regulation of interleukin-17 production” ($p = 1.4 \times 10^{-4}$). The important role of IL17 in both bacterial defense and autoimmunity suggests a key role for balancing selection in maintaining the genetic relationship between inflammation and infection, and this is reinforced by a nominal enrichment of balancing selection in loci annotated with the broader GO term “defense response to bacterium” ($p = 0.007$).

We tested for enrichment of cell-type expression specificity of genes in IBD loci in 223 distinct sets of sorted, mouse-derived immune cells from the Immunological Genome Consortium¹⁷. Dendritic cells showed the strongest enrichment, followed by weaker signals that support the GO analysis, including CD4+ T, NK and NKT cells (Figure 2C). Notably, several of these cell types express genes near our IBD associations much more specifically when stimulated; our strongest signal, a lung-derived dendritic cell, had $p_{\text{stimulated}} < 1 \times 10^{-6}$ compared with $p_{\text{unstimulated}} = 0.0015$, consistent with an important role for cell activation.

To further our goal of identifying likely causal genes within our susceptibility loci and to elucidate networks underlying IBD pathogenesis, we screened the associated genes against 211 co-expression modules identified from weighted gene co-expression network analyses¹⁸, conducted with large gene expression datasets from multiple tissues^{19–21}. The most significantly enriched module comprised 523 genes from omental adipose tissue collected from morbidly obese patients¹⁹, which was found to be 2.9-fold enriched for genes in the IBD-associated loci ($p = 1.1 \times 10^{-13}$, Supplementary Table 6, Supplementary Figure 12). We constructed a probabilistic causal gene network using an integrative Bayesian network reconstruction algorithm^{22–24} which combines expression and genotype data to infer the direction of causality between genes with correlated expression. The intersection of this network and the genes in the IBD-enriched module defined a sub-network of genes enriched in bone marrow-derived macrophages ($p < 10^{-16}$) and is suggestive of dynamic interactions relevant to IBD pathogenesis. In particular, this sub-network featured close proximity amongst genes connected to host interaction with bacteria, notably *NOD2*, *IL10*, and *CARD9*.

A *NOD2*-focused inspection of the sub-network prioritizes multiple additional candidate genes within IBD-associated regions. For example, a cluster near *NOD2* (Figure 2D) contains multiple IBD genes implicated in M.tb response, including *SLC11A1*, *VDR* and *LGALS9*. Furthermore, both *SLC11A1* (also known as *NRAMP1*) and *VDR* have been

associated with *M.tb* infection by candidate gene studies^{25–26}, and *LGALS9* modulates mycobacteriosis²⁷. Of interest, *HCK* (located in our new locus on chromosome 20 at 30.75Mb) is predicted to upregulate expression of both *NOD2* and *IL10*, an anti-inflammatory cytokine associated with Mendelian²⁸ and non-Mendelian IBD²⁹. *HCK* has been linked to alternative, anti-inflammatory activation of monocytes (M2 macrophages)³⁰; while not identified in our aforementioned analyses, these data implicate *HCK* as the causal gene in this new IBD locus.

We report one of the largest genetic experiments involving a complex disease undertaken to date. This has increased the number of confirmed IBD susceptibility loci to 163, most of which are associated with both CD and UC, and is substantially more than reported for any other complex disease. Even this large number of loci explains only a minority of the variance in disease risk, which suggests that other factors such as rarer genetic variation not captured by GWAS or environmental exposures make substantial contributions to pathogenesis. Most of the evidence relating to possible causal genes points to an essential role for host defence against infection in IBD. In this regard the current results focus ever closer attention on the interaction between the host mucosal immune system and microbes both at the epithelial cell surface and within the gut lumen. In particular, they raise the question, in the context of this burden of IBD susceptibility genes, as to what triggers components of the commensal microbiota to switch from a symbiotic to a pathogenic relationship with the host. Collectively, our findings have begun to shed light on these questions and provide a rich source of clues to the pathogenic mechanisms underlying this archetypal complex disease.

METHODS SUMMARY

We conducted a meta-analysis of GWAS datasets after imputation to the HapMap3 reference set, and aimed to replicate in the Immunochip data any SNPs with $p < 0.01$. We compared likelihoods of different disease models to assess whether each locus was associated with CD, UC or both. We used databases of eQTL SNPs and coding SNPs in linkage disequilibrium with our hit SNPs, as well as the network tools GRAIL and DAPPLE, and a co-expression network analysis to prioritize candidate genes in our loci. Gene Ontology, ImmGen mouse immune cell expression resource, the TreeMix selection software, and a Bayesian causal network analysis were used to functionally annotate these genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all the subjects who contributed samples and the physicians and nursing staff who helped with recruitment globally. UK case collections were supported by the National Association for Colitis and Crohn's disease, Wellcome Trust grant 098051 (LJ, CAA, JCB), Medical Research Council UK, the Catherine McEwan Foundation, an NHS Research Scotland career fellowship (RKR), Peninsular College of Medicine and Dentistry, Exeter, the National Institute for Health Research, through the Comprehensive Local Research Network and through Biomedical Research Centre awards to Guy's & St. Thomas' National Health Service Trust, King's College London, Addenbrooke's Hospital, University of Cambridge School of Clinical Medicine and to the University of Manchester and Central Manchester Foundation Trust. The British 1958 Birth Cohort DNA collection was funded by Medical Research Council grant G0000934 and Wellcome Trust grant 068545/Z/02, and the UK National Blood Service controls by the Wellcome Trust. The Wellcome Trust Case Control Consortium projects were supported by Wellcome Trust grants 083948/Z/07/Z, 085475/B/08/Z and 085475/Z/08/Z. North American collections and data processing were supported by funds to the NIDDK IBD Genetics Consortium which is funded by the following grants: DK062431 (SRB), DK062422 (JHC), DK062420 (RHD), DK062432 (JDR), DK062423 (MSS), DK062413 (DPM), DK076984 (MJD), DK084554 (MJD and DPM) and DK062429 (JHC). Additional

funds were provided by funding to JHC (DK062429-S1 and Crohn's & Colitis Foundation of America, Senior Investigator Award (5-2229)), and RHD (CA141743). KYH is supported by the NIH MSTP TG T32GM07205 training award. Cedars-Sinai is supported by USPHS grant PO1DK046763 and the Cedars-Sinai F. Widjaja Inflammatory Bowel and Immunobiology Research Institute Research Funds, National Center for Research Resources (NCRR) grant M01-RR00425, UCLA/Cedars-Sinai/Harbor/Drew Clinical and Translational Science Institute (CTSI) Grant [UL1 TR000124-01], the Southern California Diabetes and Endocrinology Research Grant (DERC) [DK063491], The Helmsley Foundation (DPM) and the Crohn's and Colitis Foundation of America (DPM). RJX and ANA are funded by DK83756, AI062773, DK043351 and the Helmsley Foundation. The Netherlands Organization for Scientific Research supported RKW with a clinical fellowship grant (90.700.281) and CW (VICI grant 918.66.620). CW is also supported by the Celiac Disease Consortium (BSIK03009). This study was also supported by the German Ministry of Education and Research through the National Genome Research Network, the Popgen biobank, through the Deutsche Forschungsgemeinschaft (DFG) cluster of excellence 'Inflammation at Interfaces' and DFG grant no. FR 2821/2-1. S Brand was supported by (DFG BR 1912/6-1) and the Else-Kröner-Fresenius-Stiftung (Else Kröner-Exzellenzstipendium 2010_EKES.32). Italian case collections were supported by the Italian Group for IBD and the Italian Society for Paediatric Gastroenterology, Hepatology and Nutrition and funded by the Italian Ministry of Health GR-2008-1144485. Activities in Sweden were supported by the Swedish Society of Medicine, Ihre Foundation, Örebro University Hospital Research Foundation, Karolinska Institutet, the Swedish National Program for IBD Genetics, the Swedish Organization for IBD, and the Swedish Medical Research Council. DF and SV are senior clinical investigators for the Funds for Scientific Research (FWO/FNRS) Belgium. We acknowledge a grant from Viborg Regional Hospital, Denmark. VA was supported by SHS Aabenraa, Denmark. We acknowledge funding provided by the Royal Brisbane and Women's Hospital Foundation, National Health and Medical Research Council, Australia and by the European Community (5th PCRD). We gratefully acknowledge the following groups who provided biological samples or data for this study: the Inflammatory Bowel in South Eastern Norway (IBSEN) study group, the Norwegian Bone Marrow Donor Registry (NMBDR), the Avon Longitudinal Study of Parents and Children, the Human Biological Data Interchange and Diabetes UK, and Banco Nacional de ADN, Salamanca. This research also utilizes resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the NIDDK, NIAID, NHGRI, NICHD, and JDRF and supported by U01 DK062418. The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.

References

1. Molodecky NA, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012; 142:46–54. [PubMed: 22001864]
2. Anderson CA, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet*. 2011; 43:246–252. [PubMed: 21297633]
3. Franke A, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet*. 2010; 42:1118–1125. [PubMed: 21102463]
4. Khor BGA, Xavier RJ. Genetics pathogenesis of inflammatory bowel disease. *Nature*. 2011; 474:307–317. [PubMed: 21677747]
5. Cho JH, Gregersen PK. Genomics and the multifactorial nature of human autoimmune disease. *N Engl J Med*. 2011; 365:1612–1623. [PubMed: 22029983]
6. Cortes A, Brown MA. Promise and pitfalls of the Immunochip. *Arthritis Res Ther*. 2011; 13:101. [PubMed: 21345260]
7. Zuk O, Hechter E, Sunyaev SR, Lander ES. The mystery of missing heritability: Genetic interactions create phantom heritability. *Proc Natl Acad Sci USA*. 2012; 109:1193–1198. [PubMed: 22223662]
8. Raychaudhuri S, et al. Identifying relationships among genomic disease regions: predicting genes at pathogenic SNP associations and rare deletions. *PLoS Genet*. 2009; 5:e1000534.10.1371/journal.pgen.1000534 [PubMed: 19557189]
9. Hindorff LA, et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc Natl Acad Sci USA*. 2009; 106:9362–9367. [PubMed: 19474294]
10. International Union of Immunological Societies Expert Committee on Primary I et al. Primary immunodeficiencies: 2009 update. *J Allergy Clin Immunol*. 2009; 124:1161–1178. [PubMed: 20004777]

11. Bustamante J, Picard C, Boisson-Dupuis S, Abel L, Casanova JL. Genetic lessons learned from X-linked Mendelian susceptibility to mycobacterial diseases. *Ann NY Acad Sci.* 2011; 1246:92–101. [PubMed: 22236433]
12. Patel SY, Doffinger R, Barcenas-Morales G, Kumararatne DS. Genetically determined susceptibility to mycobacterial infection. *J Clin Pathol.* 2008; 61:1006–1012. [PubMed: 18326015]
13. Zhang F, et al. Identification of two new loci at IL23R and RAB32 that influence susceptibility to leprosy. *Nat Genet.* 2011; 43:1247–1251. [PubMed: 22019778]
14. Holland SM, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med.* 2007; 357:1608–1619. [PubMed: 17881745]
15. Minegishi Y, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature.* 2007; 448:1058–1062. [PubMed: 17676033]
16. Glocker EO, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med.* 2009; 361:1727–1735. [PubMed: 19864672]
17. Hu X, et al. Integrating autoimmune risk loci with gene-expression data identifies specific pathogenic immune cell subsets. *Am J Hum Genet.* 2011; 89:496–506. [PubMed: 21963258]
18. Zhang B, Horvath S. A general framework for weighted gene co-expression network analysis. *Stat Appl Genet Mol Biol.* 2005; 4:Article17. [PubMed: 16646834]
19. Greenawalt DM, et al. A survey of the genetics of stomach, liver, and adipose gene expression from a morbidly obese cohort. *Genome Res.* 2011; 21:1008–1016. [PubMed: 21602305]
20. Emilsson V, et al. Genetics of gene expression and its effect on disease. *Nature.* 2008; 452:423–428. [PubMed: 18344981]
21. Schadt EE, et al. Mapping the genetic architecture of gene expression in human liver. *PLoS Biol.* 2008; 6:e107. [PubMed: 18462017]
22. Chen Y, et al. Variations in DNA elucidate molecular networks that cause disease. *Nature.* 2008; 452:429–435. [PubMed: 18344982]
23. Zhong H, et al. Liver and adipose expression associated SNPs are enriched for association to type 2 diabetes. *PLoS Genet.* 2010; 6:e1000932. [PubMed: 20463879]
24. Zhu J, et al. Increasing the power to detect causal associations by combining genotypic and expression data in segregating populations. *PLoS Comput Biol.* 2007; 3:e69.10.1371/journal.pcbi.0030069 [PubMed: 17432931]
25. Lewis SJ, Baker I, Davey Smith G. Meta-analysis of vitamin D receptor polymorphisms and pulmonary tuberculosis risk. *Int J Tuberc Lung Dis.* 2005; 9:1174–1177. [PubMed: 16229232]
26. Li X, et al. SLC11A1 (NRAMP1) polymorphisms and tuberculosis susceptibility: updated systematic review and meta-analysis. *PloS One.* 2011; 6:e15831.10.1371/journal.pone.0015831 [PubMed: 21283567]
27. Kumar D, et al. Genome-wide analysis of the host intracellular network that regulates survival of *Mycobacterium tuberculosis*. *Cell.* 2010; 140:731–743. [PubMed: 20211141]
28. Glocker EO, et al. Infant colitis--it's in the genes. *Lancet.* 2010; 376:1272. [PubMed: 20934598]
29. Franke A, et al. Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility. *Nat Genet.* 2008; 40:1319–1323. [PubMed: 18836448]
30. Bhattacharjee A, Pal S, Feldman GM, Cathcart MK. Hck is a key regulator of gene expression in alternatively activated human monocytes. *J Biol Chem.* 2011; 286:36709–36723. [PubMed: 21878628]

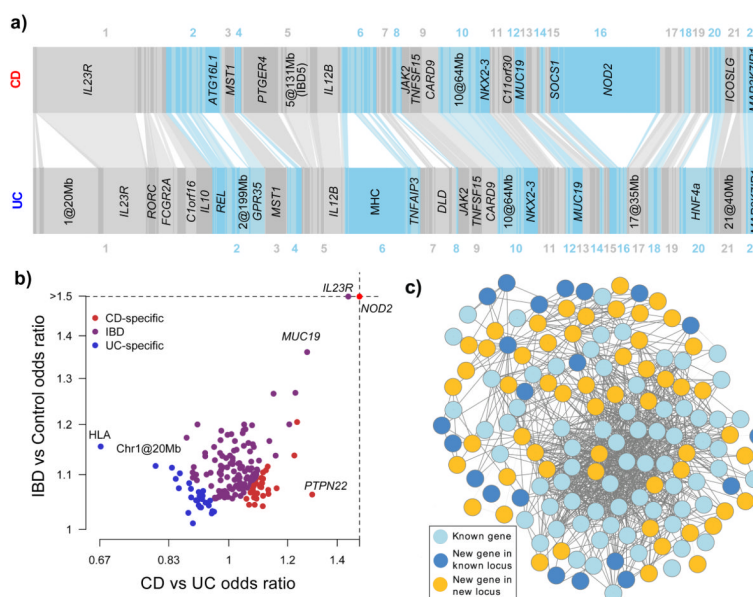


Figure 1. The IBD genome

A) Variance explained by the 163 IBD loci. Each bar, ordered by genomic position, represents an independent locus. The width of the bar is proportional to the variance explained by that locus in CD and UC. Bars are connected together if they are identified as being associated with both CD and UC. Loci are labeled if they explain more than 1% of the total variance explained by all loci for that phenotype. B) The 193 independent signals, plotted by total IBD odds ratio and phenotype specificity (measured by the odds ratio of CD relative to UC), and colored by their IBD phenotype classification from Table 1. Note that many loci (e.g. IL23R) show very different effects in CD and UC despite being strongly associated to both. C) GRAIL network for all genes with GRAIL $p < 0.05$. Genes included in our previous GRAIL networks in CD and UC are shown in light blue, newly connected genes in previously identified loci in dark blue, and genes from newly associated loci in gold. The gold genes reinforce the previous network (light blue) and expand it to include dark blue genes.

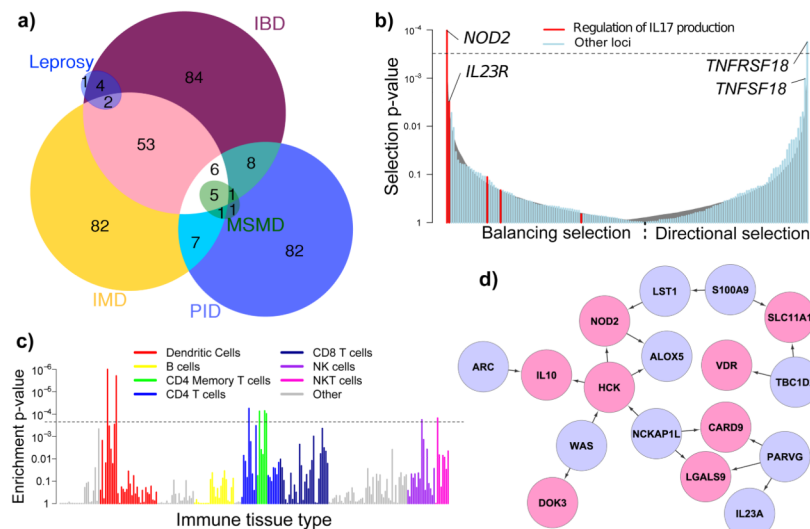


Figure 2. Dissecting the biology of IBD

A) Number of overlapping IBD loci with other immune-mediated diseases (IMD), leprosy, and Mendelian primary immunodeficiencies (PID). Within PID, we highlight Mendelian susceptibility to mycobacterial disease (MSMD). B) Signals of selection at IBD SNPs, from strongest balancing on the left to strongest directional on the right. The grey curve shows the 95% confidence interval for randomly chosen frequency-matched SNPs, illustrating our overall enrichment ($p = 5.5 \times 10^{-6}$), while the dashed line represents the Bonferroni significance threshold. SNPs highlighted in red are annotated as involved in regulation of IL17 production, a key IBD functional term related to bacterial defense, and are enriched for balancing selection. C) Evidence of enrichment in IBD loci of differentially expressed genes from various immune tissues. Each bar represents the empirical p-value in a single tissue, and the colours represent different cell type groupings. The dashed line is Bonferroni-corrected significance for the number of tissues tested. D) NOD2-focused cluster of the IBD causal subnetwork. Pink genes are in IBD associated loci, blue are not. Arrows indicate inferred causal direction of regulation of expression.

Table 1

Crohn's disease-specific, ulcerative colitis-specific and IBD general loci

Chr	Position (hg19 (Mb))	SNP	Key Genes (+N additional in locus)
Crohn's Disease			
1	78.62	rs17391694	(5)
1	114.3	rs6679677[§]	PTPN22 /(8)
1	120.45	rs3897478	ADAM30,(5)
1	172.85	rs9286879	FASLG,TNFSF18 ,(0)
2	27.63	rs1728918	UCN,(23)
2	62.55	rs10865331	(3)
2	231.09	rs6716753	SP140,(5)
2	234.15	rs12994997	ATG16L1 /(8)
4	48.36	rs6837335	(6)
4	102.86	rs13126505	(1)
5	55.43	rs10065637	IL6ST,IL31RA ,(1)
5	72.54	rs7702331	(4)
5	173.34	rs17695092	CPEB4,(2)
6	21.42	rs12663356	(3)
6	31.27	rs9264942	(22)
6	127.45	rs9491697	(3)
6	128.24	rs13204742	(2)
6	159.49	rs212388	TAGAP,(5)
7	26.88 [‡]	rs10486483	(2)
7	28.17	rs864745	CREB5,JAZF1,(1)
8	90.87	rs7015630	RIPK2,(4)
8	129.56	rs6651252	0
13	44.45	rs3764147	LACC1,(3)
15	38.89	rs16967103	RASGRP1,SPRED1 ,(2)
16	50.66 ^{**}	rs2066847[§]	NOD2 /(6)
17	25.84	rs2945412	LGALS9,NOS2 ,(3)
19	1.12	rs2024092	GPX4,HMHA1,(20)
19	46.85 [‡]	rs4802307	(9)
19	49.2	rs516246	FUT2, (25)
21	34.77	rs2284553	IFNGR2,IFNAR1 , (10)
Ulcerative Colitis			
1	2.5	rs10797432	TNFRSF14 , (10)
1	20.15 ^{**}	rs6426833	(9)
1	200.09	rs2816958	(3)
2	198.65	rs1016883	RFTN2,PLCL1,(7)
2	199.70 [*]	rs17229285	0

Chr	Position (hg19 (Mb))	SNP	Key Genes (+N additional in locus)
3	53.05	rs9847710	PRKCD,ITIH4,(8)
4	103.51	rs3774959	NFKB1,MANBA,(2)
5	0.59	rs11739663	SLC9A3,(8)
5	134.44	rs254560	(6)
6	32.595	rs6927022	(15)
7	2.78	rs798502	CARD11, GNA12, (5)
7	27.22 [‡]	rs4722672	(14)
7	107.45 [*]	rs4380874	DLD,(9)
7	128.57	rs4728142	IRF5 ^{//} , (13)
11	96.02	rs483905	JRKL,MAML2,(2)
11	114.38	rs561722	FAM55A,FAM55D,(5)
15	41.55	rs28374715	(11)
16	30.47	rs11150589	ITGAL,(20)
16	68.58	rs1728785	ZFP90,(6)
17	70.64	rs7210086	(3)
19	47.12 [‡]	rs1126510	CALM3,(14)
20	33.8	rs6088765	(11)
20	43.06	rs6017342	ADA,HNF4A,(9)
Inflammatory Bowel Disease			
1	1.24	rs12103	TNFRSF18,TNFRSF4,(30)
1	8.02	rs35675666	TNFRSF9,(6)
1	22.7	rs12568930 [‡]	(3)
1	67.68 ^{**}	rs11209026 [‡]	IL23R ^{//} , (5)
1	70.99	rs2651244 [‡]	(3)
1	151.79	rs4845604 [‡]	RORC,(14)
1	155.67	rs670523 [‡]	(31)
1	160.85	rs4656958 [‡]	CD48, (15)
1	161.47	rs1801274 [‡]	FCGR2A/B, FCGR3A, (13)
1	197.6	rs2488389	C1orf53,(2)
1	200.87	rs7554511	KIF21B,(6)
1	206.93	rs3024505 [‡]	IL10, (10)
2	25.12	rs6545800 [‡]	ADCY3,(6)
2	28.61	rs925255 [‡]	FOSL2,BRE,(1)
2	43.81	rs10495903 [‡]	(5)
2	61.2	rs7608910	REL, (9)
2	65.67	rs6740462	SPRED2,(1)
2	102.86 [*]	rs917997 [‡]	IL18RAP, IL1R1, (7)
2	163.1	rs2111485	IFIH1,(5)

Chr	Position (hg19 (Mb))	SNP	Key Genes (+N additional in locus)
2	191.92	rs1517352	STAT1,STAT4,(2)
2	219.14	rs2382817	(15)
2	241.57 *	rs3749171 †	GPR35,(12)
3	18.76	rs4256159 †	0
3	48.96 **	rs3197999	MST1, PFKB4, (63)
4	74.85	rs2472649 †	(11)
4	123.22	rs7657746	IL2,IL21,(2)
5	10.69	rs2930047	DAP,(2)
5	40.38 **	rs11742570 †	PTGER4,(1)
5	96.24	rs1363907	ERAP2, ERAP1, (3)
5	130.01	rs4836519 †	(1)
5	131.19 *	rs2188962 †	IBD5 locus, (18)
5	141.51	rs6863411 †	SPRY4,NDFIP1,(5)
5	150.27	rs11741861 †	IRGM//,(10)
5	158.8 **	rs6871626 †	IL12B,(3)
5	176.79	rs12654812	DOK3,(17)
6	14.71	rs17119	0
6	20.77 *	rs9358372 †	(2)
6	90.96	rs1847472	(1)
6	106.43	rs6568421 †	(2)
6	111.82	rs3851228	TRAF3IP2, (4)
6	138	rs6920220 †	TNFAIP3,(1)
6	143.9	rs12199775	PHACTR2,(5)
6	167.37	rs1819333 †	CCR6,RPS6KA2,(4)
7	50.245 *	rs1456896	ZPBP,IKZF1,(4)
7	98.75	rs9297145	SMURF1,(6)
7	100.34	rs1734907 †	EPO,(21)
7	116.89	rs38904 †	(6)
8	126.53	rs921720 †	TRIB1,(1)
8	130.62	rs1991866	(2)
9	4.98	rs10758669	JAK2,(4)
9	93.92	rs4743820 †	NFIL3,(2)
9	117.60 **	rs4246905	TNFSF15, (4)
9	139.32 *	rs10781499 †	CARD9, (22)
10	6.08	rs12722515 †	IL2RA,IL15RA,(6)
10	30.72	rs1042058 †	MAP3K8,(3)
Inflammatory Bowel Disease			

Chr	Position (hg19 (Mb))	SNP	Key Genes (+N additional in locus)
10	35.3	rs11010067 [†]	CREM ,(3)
10	59.99	rs2790216	CISD1,IPMK,(2)
10	64.51 ^{**}	rs10761659 [†]	(3)
10	75.67	rs2227564 [†]	(13)
10	81.03	rs1250546 [†]	(5)
10	82.25	rs6586030 [†]	TSPAN14,C10orf58,(4)
10	94.43	rs7911264	(4)
10	101.28	rs4409764	NKX2-3,(6)
11	1.87	rs907611	TNNI2,LSP1 ,(17)
11	58.33	rs10896794	CNTF,LPXN,(8)
11	60.77	rs11230563	CD6 , (14)
11	61.56	rs4246215 [†]	(15)
11	64.12	rs559928	CCDC88B ,(23)
11	65.65	rs2231884 [†]	RELA, (25)
11	76.29	rs2155219 [†]	(5)
11	87.12	rs6592362	(1)
11	118.74	rs630923 [†]	CXCR5,(17)
12	12.65	rs11612508 [†]	LOH12CR1,(8)
12	40.77 [*]	rs11564258 [†]	MUC19,(1)
12	48.2	rs11168249 [†]	VDR,(8)
12	68.49	rs7134599 [†]	IFNG , (3)
13	27.52	rs17085007 [†]	(2)
13	40.86 ^{**}	rs941823 [†]	(3)
13	99.95	rs9557195	GPR183,GPR18,(6)
14	69.27	rs194749 [†]	ZFP36L1,(4)
14	75.7	rs4899554 [†]	FOS,MLH3 ,(6)
14	88.47	rs8005161	GPR65,GALC ,(1)
15	67.43	rs17293632 [†]	SMAD3,(2)
15	91.17	rs7495132	CRTC3,(3)
16	11.54 [*]	rs529866 [†]	SOCS1,LITAF , (11)
16	23.86	rs7404095	PRKCB ,(5)
16	28.6	rs26528 [†]	IL27, (14)
16	86	rs10521318 [†]	IRF8,(4)
17	32.59	rs3091316 [†]	CCL13,CCL2 , (5)
17	37.91	rs12946510	ORMDL3, (16)
17	40.53	rs12942547 [†]	STAT3 , (15)
17	57.96	rs1292053 [†]	TUBD1,RPS6KB1,(9)
18	12.8	rs1893217 [†]	(6)

Chr	Position (hg19 (Mb))	SNP	Key Genes (+N additional in locus)
18	46.39	rs7240004 [†]	SMAD7,(2)
18	67.53	rs727088	CD226 ,(2)
19	10.49 [*]	rs11879191	TYK2 , (27)
19	33.73	rs17694108	CEBPG,(8)
19	55.38	rs11672983	(19)
20	30.75	rs6142618 [‡]	HCK,(10)
20	31.37	rs4911259	DNMT3B,(8)
20	44.74	rs1569723 [‡]	CD40 , (13)
20	48.95	rs913678	CEBPB,(5)
20	57.82	rs259964	ZNF831,CTSZ,(5)
20	62.34	rs6062504	TNFRSF6B, (26)
21	16.81	rs2823286 [‡]	0
21	40.46	rs2836878 [‡]	(3)
21	45.62	rs7282490	ICOSLG,(9)
22	21.92	rs2266959	(13)
22	30.43	rs2412970	LIF , OSM , (9)
22	39.69 [*]	rs2413583 [‡]	(19)

The position given is the middle of the locus window.

^{*} = additional genome-wide significant associated SNP in the region.

^{**} = two or more additional genome-wide significant SNPs in the region.

[†] = These regions have overlapping but distinct UC and CD signals.

[‡] = heterogeneity of odds ratios.

[§] = CD risk allele is significantly protective in UC.

// = gene for which functional studies of associated alleles have been reported. Newly discovered loci. Bolded rs numbers indicate SNPs with p-values less than 10^{-13} . Listed are genes implicated by one or more candidate genes approaches. Bolded genes have been implicated by two or more candidate gene approaches. For each locus, the top two candidate genes are listed. A complete listing of gene prioritization is provided in Supplementary Table 2.